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Original Research

Antiepileptic activity of Essential Oil isolated from *Commiphora Myrrha* resin and its effect on brain GABA level

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Abstract

Aim: The present study was undertaken to investigate the antiepileptic activity of the essential oil of the Oleo-gum-resin obtained from Commiphora Myrrha (CM) resins.

Material and Methods: The essential oil from Commiphora Myrrha (EOCM) was isolated using the Clevenger apparatus. The anticonvulsant effect was examined against pentylenetetrazole (PTZ), strychnine, and maximal-electroshock (MES)-induced acute convulsions in mice. Flumazenil and diazepam were added to establish the anticonvulsant mechanism of EOCM. To understand the effect of EOCM on brain GABA level, intact mice brains were harvested and GABA level was determined.

Results: EOCM has shown the maximum decline in spontaneous motor activity at 2 hours. EOCM has not shown any protection against the strychnine-induced model. In the PTZ model, mice treated with EOCM at medium ($p<0.01$) and high dose ($p<0.001$) have shown a significant and dose-dependent increase in the latency of tonic convulsions and a decline in % mortality compared to the control group. Against the MES model, EOCM at medium ($p<0.05$) and high doses ($p<0.01$) have shown a significant decline in the length of hind-limb tonic extension (HLTE) and % mortality compared to the control group. A high dose of EOCM + diazepam (0.5 mg/kg/bw) has shown a synergistic effect. Flumazenil drastically reverses the protection offered by EOCM and diazepam. Moreover, EOCM plain has increased GABA levels in the brain.

Discussion: EOCM is very useful in the control of clonic seizures, and the effect is related to the GABA-A receptor Cl^- channel modulating property and partly by increasing GABA levels in the brain.

Keywords

Acute seizure; Commiphora Myrrha; Essential Oils; Maximal-Electroshock; Pentylenetetrazole; Strychnine

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Introduction

Worldwide, nearly 20-30% of patients suffer from seizures due to epilepsy, and around 20% of patients remain refractory to currently available antiepileptic drugs (AEDs) [1, 2]. Recently, extensive research on the medical plants and their isolated compounds has been carried out that may provide new potent and alternative treatment options for the management of various types of CNS disorders [3]. Certain types of aromatic plants are used in medicine because of their essential oils (EOs) and/or phytochemical elements as main elements. In many cultures, including the Middle-East, India, China, and Brazil, EOs have been used as anticonvulsants in traditional medicine [4]. Moreover, recent findings on EOs and their main elements have caught our attention to screen aromatic plants to elucidate their scientific and biological aspects, which could provide us a lead molecule with advantages over synthetic AED [5].

One such herb, Commiphora Myrrha, CM (family: Burseraceae) grows in the Middle-east and Africa and has a long history of medicinal application [6, 7]. Phytochemical screening of myrrh showed the presence of 3–8% essential oils, 30–60% water-soluble gum, and 25–40% alcohol-soluble resins beside a series of metabolites including terpenoids, steroids, flavonoids, lignans, carbohydrates, and long-chain aliphatic alcohol derivatives were reported in Commiphora species [8].

Based upon the traditional claim, the presence of essential oils in the CM, makes the plant venerable for the scientific evaluation. The anti-epileptic activity of EOs isolated from an oleo-gum resin derived from CM was screened epilepsy models with chemoconvulsant (PTZ and strychnine) and electrical stimulation (maximum electric shock).

Material and Methods

Materials

Instruments: Clevenger apparatus, heating mantle, condenser, electro convulsometer (model no: MI.PH-1017), actophotometer (model no:MA-123).

Chemicals: Diazepam, pentylenetetrazole (PTZ), strychnine and flumazenil were purchased from Sigma Aldrich, USA.

Plant authentication

Arial parts of the CM were collected during the middle age of the plant from the Northern region of Saudi Arabia and verified by the Department of Natural products, Northern Border University and a duplicate herbarium was also retained (NBU/NP/2019-07) in the department.

Collection

The oleo-gum resin of CM was collected from the cracks formed in the bark of the tree between January and February 2020, shade dried for a week and washed with distilled water to remove the unwanted debris.

Extraction of Essential Oil from CM resin

The dried oleo-gum of CM was powered with a pulverizer. The powered resin was then passed through sieve #40 to get a fine powder and processed for EOs separation.

Powdered resin (100 g) was loaded in the 1000 ml round bottom flask (RBF) along with 500 ml of distilled water. Clevenger's apparatus was attached to the RBF and the temperature of the heating mantle was set to around 160±1oC. The heating mantle was started until the content of the RBF begins to boil; vapors were condensed to cool back into liquid form. At the outlet cocks of Clevenger apparatus, EOs floats on the water. The total amount of separated EO, measured on Clevenger's apparatus scale, was 0.9 ml as per the method reported by Costa et al. in 2014 [9]. The volatile oil was carefully collected in a sealed bottle and stored at -4O C for further use.

Pharmacological Evaluation of EOCM

Acute Toxicity tests:

In vivo testing for the acute oral toxicity was carried out as per the OECD (Organization for Economic and Cooperation Development) section 15-423 guidelines [Available at websitehttps://doi.org/10.1787/9789264071001-en].

A random sampling technique was employed to select animals for toxicity testing. Female albino mice (n=6) weighing 20-22g were fasted for 4 hours with free access to water only. The animals were divided into 2 groups (n=3), and all the mice were treated only once. Group 1 (control group) was administered with 10ml/kg/bw of maze-oil, while Group 2 (test) was treated with 10ml/kg/bw of extracted essential oil of CM (EOCM), diluted with 1ml of maze-oil p.o. Doses were selected based upon the maximum oral dose-volume, which must not exceed 1 ml/100 gm/bw of the mice. Later, mortality was observed in both the groups for the next 8 hours and once daily for the next 14 days, during this period no drugs were administered. During this period, the animals were observed for any signs of behavioral changes including locomotor activity (lethargy), lacrimation, salivation, defecation, the color of the fur, abdominal respiration, grooming, body weight changes, mortality, etc. (Table 1). Based on the results of acute toxicity testing, a dose of 2.5ml/kg/bw was selected as the median dose, and the other 2 doses were 1ml/kg/bw and 5ml/kg/bw as sub-max and super-max, respectively [10].

Experimental Animals

Official permission was obtained from the Institutional Animal Ethics Committee (IAEC) of the Faculty of Pharmacy, Northern Border University (permission number HAP-09-A-043). Swiss albino mice were strictly handled as per the guidelines mentioned by the National Committee of Bioethics (NCBE).

Spontaneous locomotor activity (SMA)

The mice were divided into two groups (n=6). Group 1 received 5ml/kg/bw of EOCM mixed with maze-oil and Group 2 received 5ml/kg/bw of maze-oil only. Treatment in both the groups was by p.o. route. Immediately after the oral administration, the mice were individually placed in an activity cage (actophotometer), and SMA was recorded for 5min. The procedure was repeated for all the animals (Groups 1 and 2), by resetting the counter to zero. The recording was done six times with an interval of 30 minutes (0, 30, 90, 120, 150 and 180min) [11].

Pentylenetetrazole-induced convulsions

A fresh lot of Swiss albino mice weighing 22-24 g were procured from the Central animal house facility at Northern Border University and acclimatized for the next 10 days. The animals were divided into 7 groups (n=8). Group-1, as control (maze-oil, 5ml/kg/bw, p.o) Groups 2 and 3 were treated with diazepam 0.5 and 1 mg/kg/bw, i.p. respectively, whereas Groups 4, 5, and 6 were treated with 1, 2.5, and 5 ml/kg/bw EOCM, respectively. Group 7 received diazepam 0.5mg/kg/bw + EOCM 5ml/kg/bw. All the test and standard groups were treated with PTZ (80mg/

Table 1. Acute Toxicity Record Sheet

Sl. No	Drug	Toxicity		Time of Death	Observations									
		On Set	Stop		Skin & Fur	Eyes	Resp	CNS	Tre	Con	Sali	Diah	Sleep	Let	Coma
1	EOCM	x	x	x	x	x	x	x	x	x	x	x	x	√	x
2	MO	x	x	x	x	x	x	x	x	x	x	x	x	x	x

Drug: EOCM ; Dose: 10 ml/kg/bw; Frequency: Once; Species: Swiss Albino Mice; Gender: Female (*TRE-Tremor, CON-Convulsions, SALI- Salivation, Diah - Diarrhea, LET-Lethargy)
x = Negative, √= Positive; MO = Maze Oil; EOCM = Essential oil of *Commiphora Myrrha*

kg//bw, i.p.) after 2 hours and 30 minutes, respectively.

Immediately after PTZ administration, the mice were observed for the latency of clonic convulsions and mortality protection for the next 60 minutes. The ability of the EOCM to prevent or delay the onset of the hind-limb extension and to reduce mortality was taken as an indication of anticonvulsant activity [12].

Effect of flumazenil + EOCM on PTZ-induced convulsions

To understand the protective effect of EOCM against PTZ-induced convulsion, we have used flumazenil as a GABA-A receptor antagonist. Thirty-two, male Swiss albino mice were divided into 4 groups (n=8). Group 2 was treated with flumazenil (2mg/kg/bw, i.p.), 5 minutes before the administration of diazepam (0.5mg/kg, i.p.) and PTZ was administered after 30 minutes. For Group 3, the same protocol was followed with the high-dose of diazepam (1mg/kg/bw, i.p.). In Group 4, flumazenil was administered 30 minutes before PTZ administration. In Group 5, flumazenil (2mg/kg/bw, i.p.) was administered 5 minutes before EOCM and 2 hours before PTZ administration [13].

Strychnine-induced convulsions

Another fresh lot of the Swiss Albino mice weighing 22-24g were used to test the EOCM against strychnine-induced epilepsy. The mice were divided into 5 groups (n=8). Group 1 was the control (maze-oil, 1ml/kg/bw, p.o.), Group 2 was used as a standard (diazepam, 0.5mg/kg/bw, i.p.), Groups 3, 4 and 5 were labeled as a test, treated with 1, 2.5 and 5ml/kg/bw of EOCM. Strychnine (2mg/kg/bw, i.p.) was injected i.p to the mice 30 minutes after vehicle/extracts/standard drug administration. The latency to the first convulsion and the percentage of mortality were recorded for 30 minutes. Animals surviving more than 30 minutes were considered to be protected [14].

Maximum Electroshock (MES)-induced seizures

The tonic convulsion of the hind-limb extremities of the mice was induced by passing an alternating electrical current of 50 Hz and 150 mA for 0.2 sec using electrodes in the ear pinna [16]. Another fresh lot of forty Swiss Albino mice were divided into 5 groups (n=8). Group 1 was used as normal control (maze-oil, 1ml/kg/bw, p.o.), Group 2 as a standard (diazepam, 0.5 mg/kg/bw, i.p.), and Groups 3, 4 and 5 were considered as a test, treated by 1, 2.5 and 5 ml/kg/bw of EOCM. Two hours later, after test drug administration and 45 minutes later after vehicle and standard drug administration, MES was applied. The number of animals protected from hind-limb-tonic-extension seizure (HLTE) and the time spent in this position were determined [15].

Effect of flumazenil + EOCM on MES-induced seizures

Thirty-two male Swiss albino mice were divided into 4 groups (n=8). In the second group, animals were treated with flumazenil (2mg/kg/bw, i.p.), 5 minutes before the administration of diazepam (0.5mg/kg/bw, i.p.) and 30 minutes later, MES was applied as before. In Group 3, the same protocol was followed where the dose of diazepam was 1 mg/kg/bw, i.p. In Group 4, flumazenil was administered 30 minutes before the MES. In the fifth group, animals were treated with flumazenil (2mg/kg/bw, i.p.), 5min before EOCM, and 2 hours before MES. The same parameters were recorded as before.

Determination of brain-GABA level

A separate experiment was carried out in mice to determine the effect of EOCM on the brain GABA level. The mice were divided into 4 groups, (n=6). Group 1 was treated with 5ml/kg/bw maze-oil, p.o. whereas groups 2, 3, and 4 were treated with increasing doses of EOCM i.e., 1 2.5 and 5ml/kg/bw, respectively. All the groups were treated only once, 2 hours later, all the mice were sacrificed by the cervical dislocation and the intact brain was harvested. The brain homogenate was prepared using a tissue homogenizer [16]. GABA level in the brain was estimated as per the method described by Walia et al. in 2019 [17].

Statistical Analysis

Results are expressed as means ± SEM. Comparisons between the averages of series of values were performed by ANOVA followed by Dunnett's multiple comparisons test using a Graphpad prism 9.

Results

Spontaneous Motor Activity (SMA)

Treatment with EOCM 5ml/kg/bw, p.o. represented a sharp decline in the mean SMA at 90 and 120 minutes of drug administration. The maximum CNS depressant activity was observed at 120 minutes compared to the plain maze-oil-treated group (Table 2).

Table 2. Assessment of Spontaneous motor activity (SMA) by using Actophotometer

Groups	Treatment 5 ml/kg/ bw	Motor Activity and Time intervals					
		0 hrs	30 min	90 min	120 min	150 min	180 min
1	EOCM	60.33 ± 1.22	68.33 ± 1.87	40.1 ± 1.79	19.33 ± 1.94	30.66 ± 2.52	38.83 ± 2.05
2	Maze Oil	55.48 ± 1.14	61.87 ± 1.67	68.1 ± 1.89	57.7 ± 2.94	59 ± 2.91	62.53 ± 2.31

EOCM: Essential oil of *Commiphora Myrrha*

Table 3. Effects of EOCM on GABA levels of mice brain

Group no	Treatment	Brain GABA level in µM
1	Maze oil (5 ml/kg/bw, p.o.)	20.03 ± 0.08819
2	EOCM (1 ml/kg/bw, p.o.)	20.05 ± 0.1258
3	EOCM (2.5 ml/kg/bw, p.o.)	21.48 ± 0.5918
4	EOCM (5 ml/kg/bw, p.o.)	22.25 ± 0.5830

EOCM: Essential oil of Commiphora Myrrha

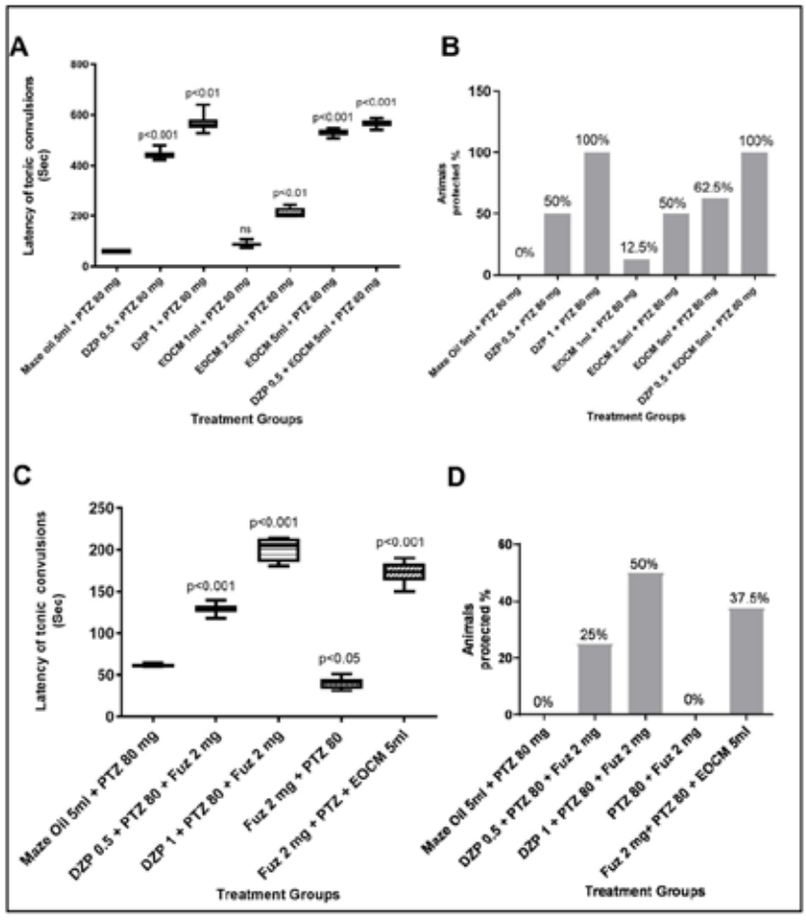

Figure 1.

A. Effect of EOCM on latency of tonic convulsions (sec) against PTZ-induced epilepsy.

B. Effect of EOCM on animals protected (%) against PTZ-induced epilepsy.

C. Effects of flumazenil + EOCM on the latency of tonic convulsions against PTZ-induced convulsion in mice.

D. Effects of flumazenil + EOCM on the animals protected (%) against PTZ-induced convulsion in mice.

Values are expressed as mean ± SEM. *** (p<0.001)

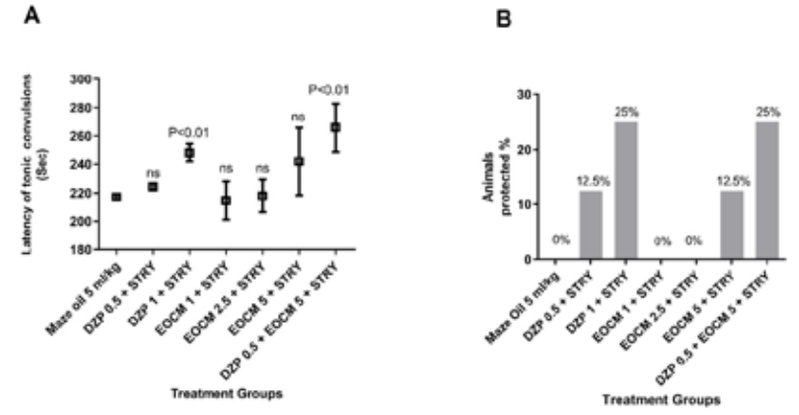

Figure 2.

A. Effect of EOCM on the latency of tonic convulsions (sec) against strychnine-induced epilepsy.

B. Effect of EOCM on animals protected (%) against strychnine-induced epilepsy.

Values are expressed as mean ± SEM. *** (p<0.001)

Effect of EOCM on PTZ-induced convulsions

Animal groups treated with EOCM at medium (p<0.01) and high dose (p<0.001) have shown a significant and dose-dependent increase in the latency of tonic convulsions compared to the control group (Figure 1A).

Mortality protection of EOCM at doses (1, 2.5, 5ml/kg/bw) were 12.5%, 50%, 62.5%, respectively. Animal group treated with diazepam 0.5mg/kg + EOCM 5ml/kg/bw has shown 100% protection, the same as the group receiving diazepam 1ml/kg/bw (Figure 1B).

Effects of flumazenil + EOCM on PTZ-induced convulsions

Flumazenil (2mg/kg/bw) + diazepam 0.5 and 1mg/kg/bw significantly (p<0.001) reverses the effect of diazepam in prolonging the latency of clonic seizure. Mice treated with flumazenil + EOCM 5ml/kg/bw significantly (p<0.001) reverses the protective effect of plain EOCM 5 ml/kg/bw. (Figure 1 C)

The animal mortality protection (%) in the maze-oil and flumazenil groups was 0% against PTZ-induced seizure. Amusingly, treatment with flumazenil + EOCM 5ml/kg/bw reduced the protection from 62.5 % to 37.5% compared to the group receiving plain EOCM 5 ml/kg/bw (Figure 1D).

Effect of EOCM on strychnine-induced convulsions

Strychnine produced tonic seizures in all groups. EOCM (1 and 2.5 ml/kg/bw) did not significantly affect the incidence of seizures and did not increase the latency of the seizure (Figure 2 A).

There was 25% protection offered by the combination of diazepam 0.5 + EOCM 5ml/kg/bw, whereas plain EOCM 5ml/kg/bw offered only 12.5 % protection (Figure 2 B).

Effect of EOCM on MES-induced seizures

Animal groups treated with EOCM at low (ns), medium (p<0.05) and high dose (p<0.01) have shown a significant decline in the length of HLTE compared to the control group. The animal group treated with a high-dose of EOCM + 0.5mg/kg/bw diazepam has shown the most significant (p<0.001) decrease in the duration of HLTE compared to the control group (Figure 3 A).

Mice treated with 0.5mg diazepam + 5ml/kg/bw EOCM have shown 100% protection against MES-induced seizures (Figure 3 B).

Effect of flumazenil + EOCM on MES-induced seizures

Flumazenil increases the duration of HLTE when added in EOCM 5ml (p<0.001) compared to plain EOCM (Figure 3C). Flumazenil reverses animal mortality (%) when administered with EOCM 5ml/kg/bw from 50% to 25% compared to the group treated with plain EOCM 5ml kg/bw (Figure 3D).

Effect of EOCM on brain-GABA level

EOCM has shown a slight but significant up-regulation in the level of GABA in the brain at medium (p<0.05) and high dose (p<0.01) compared to the control group (Table 3).

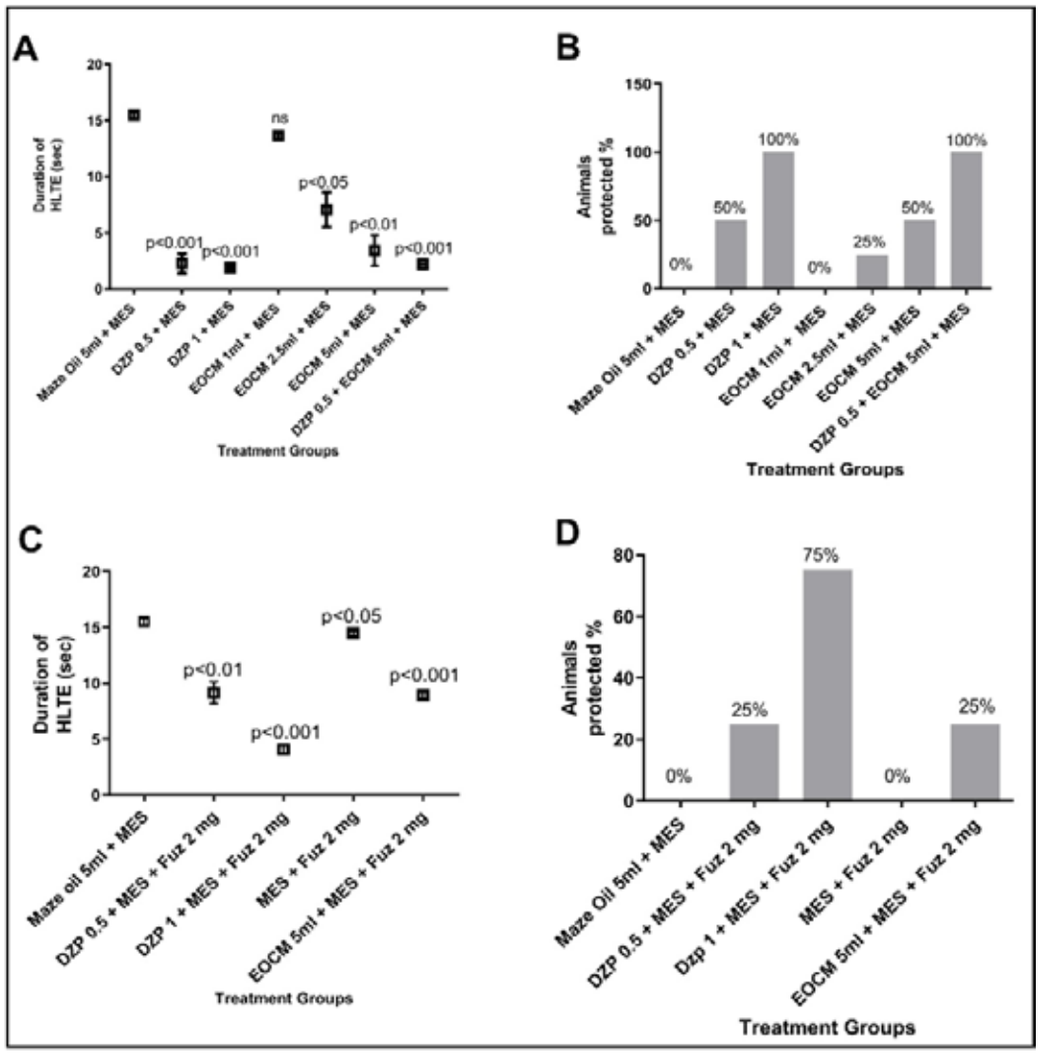

Figure 3.
A. Effect of EOCM on duration of HLTE (sec) against MES induced seizure.
B. Effects of flumazenil + EOCM on the animals protected (%) against MES-induced convulsion in mice.
C. Effects of flumazenil + EOCM on the duration of HLTE (sec) against MES-induced convulsion in mice.
D. Effects of flumazenil + EOCM on the animals protected (%) against MES-induced convulsion in mice.
Values are expressed as mean ± SEM. *** ($p<0.001$)

Discussion

The findings of the present study show that EOCM has potent anti-epileptic property against MES and PTZ-induced epilepsy, while it fails against strychnine-induced seizures. The results of the motor activity indicate the peak decline in SMA after 2 hours of EOCM administration, which gave us an idea to administer EOCM after 2 hours (where it has maximum CNS depressant activity) to induce convulsions in the mice. The normal state of the brain is maintained by a fine balance between excitatory (glutamate) and inhibitory (GABA/glycine) neurotransmitters. GABA-A- is a pentameric transmembrane Cl^- channel complex, composed of five α, β, γ subunits gated by a primary ligand (GABA) and modulated by secondary ligands, which include diazepam and few others. The binding site of the GABA is located on the β-subunit, which causes hyperpolarization (due to the influx of Cl^- ions) and decreases the firing rate of neurons [18].

It is clear that PTZ competes with GABA in the β-subunit of the GABA-A receptor Cl^- channel, whereas diazepam binds to the α/γ subunit interface of GABA-A receptor Cl^- channel and enhances the frequency of Cl^- channel opening by facilitating the effect of GABA and, hence, blunts the effect of PTZ [19]. EOCM-treated groups of animals have shown a dose-dependent increase in latency and a decrease in the mortality of the animals. There was a synergistic increase in the protection of both parameters by combining a high-dose of EOCM + 0.5 mg/kg/bw diazepam. These findings suggest that the components of EOCM may be responsible for the above action.

According to a study published by Hanus LO et al. in 2005, the results of gas chromatography of EOCM show the presence of cuminic aldehyde, eugenol, metacresol, pinene, limonene, diterpenes, and sesquiterpenes [20].

Monoterpenes like α-pinene, eugenol, and limonene have proven antiepileptic activity [21]. Past literature suggests that the α-pinene potentiates GABA by binding to the GABA-A receptor at the diazepam binding site [22]. Following our findings and to confirm the above mechanism, flumazenil (2mg/kg/bw) was added along with the high-dose of EOCM and diazepam treated groups against PTZ-induced seizures. Flumazenil blunts the anticonvulsant effect of the EOCM and diazepam treated groups. Flumazenil is a competitive antagonist of diazepam at α/γ subunit interface the function of GABA-A Cl^- channels, this fact tells us that EOCM and diazepam have the same binding site.

Strychnine is an alkaloid that causes lethal convulsions by antagonizing inhibitory glycine receptors. EOCM has not shown any protection against the strychnine-induced chemoconvulsant model, and it is stated that the protection offered by the EOCM is not via enhancing the effect of glycine.

In the third model, EOCM has shown a decrease in the duration of HLTE like diazepam treated groups in a dose-dependent manner. The protection offered by the EOCM maybe related to

the presence of eugenol [23]. It was also stated that eugenol inhibits the activity of GABA-transaminase, causes a positive GABA-shift, to confirm this, we have introduced flumazenil (2mg/kg/bw) along with a high-dose of EOCM + diazepam treated groups against MES-induced epilepsy [24]. Flumazenil drops the protection offered by the EOCM and diazepam. These findings propose a decreased level of GABA-transaminase, showing a positive GABA shift, but flumazenil competitively inhibits the binding of diazepam/EOCM to the β-subunit of the GABA-A ion-channel. Additionally, to confirm the aforementioned possibility, brain GABA levels were measured in mice treated with EOCM only. A medium and high dose of EOCM has shown a slight but significant dose-dependent rise in the GABA level. Taken together, it is suggested that EOCM might have down-regulated the GABA transaminase activity in the brain and up-regulate GABA levels, and there is also a strong probability of the agonistic activity of the EOCM to the GABA/benzodiazepine receptor complex.

There are some limitations in this study. The level of brain GABA transaminase was not taken into consideration, whereas the GABA level was estimated. Periodic estimation of GABA level at specified intervals might have answered the pick effect of EOCM on the GABA level, but based on the SMA results, GABA level was estimated only once.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

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